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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,968	GERMINO ET AL.	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,16,17,19-29,31-37,39-57,59-63,65,66,68,69 and 72-75* is/are pending in the application.

4a) Of the above claim(s) *18,30 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11,16,17,19-29,31-37,39-57,59-63,65,66,68,69 and 72-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 11/26/2004. Claims 1-4,6-11,16, 25, 26, 43-45, 60, 62, 63, 65, 68, 69, 72, and 74 have been amended, claims 5, 12-15, 38, 64, 67, 70, and 71 have been canceled, and no claims have been added. Claims 1-4,6-11,16,17,19-29,31-37,39-57,59-63,65,66,68,69 and 72-75 are pending while claims 18, 30, and 58 have been withdrawn. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Restriction/Election

Newly submitted claims 1-4, 6-11,16,17,19-29,31-37,39-57,59-63,65,66,68,69 and 72-75 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: While it was suggested in the applicant-initiated interview of 10/22/2004, that applicant include their 8 primers as a set for further prosecution, better anchoring their claims, it was not suggested that the original restriction requirement and requirement for sequence election be waived and that applicant consider pending every one of their SNPs and primer pairs individually(e.g. claim 20). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims drawn to any sequence other than to the specific SEQ ID NOS: of the 8 primers that make up the elected set of primers, are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR

1.142(b) and MPEP § 821.03. Applicant is reminded that from the FAOM(1/29/2004) in

response to applicant's initial election;

"The SEQ ID NOS: that were not elected, and claims directed to non-elected subject matter will not be examined as they are considered to be withdrawn until the time of allowance when rejoinder is possible, if warranted. Specifically, claims 18, 30, 58 and 67 are drawn to non-elected subject matter and are considered to be withdrawn. The traversal is on the ground(s) that the examiner's analysis has become tautological. Furthermore the applicant asserts that the different SEQ ID NOS; of their claims could be searched without a burden to the examiner. While the examiner acknowledges the applicants arguments, they are reminded that each of their claimed SEQ ID NOS: is patentably distinct in its structure and in its function. Additionally, a search of each and every SEQ ID NO: within the claims would in fact represent a burden on the office as the applicant has been afforded the opportunity "to include up to 10 nucleotide sequences per application" as instructed by the *Official Gazette* and notices posted on the PTO website.

The examiner retains his/her discretion in the inclusion of "up to 10 sequences." It is further maintained that the examiner adhered to the PTO policy concerning restriction practice as defined in *35 U.S.C. 121*, "if two or more independent and distinct inventions are claimed in one application, the commissioner may require the application to be restricted to one of the inventions." The examiner maintains that the inventions are distinct, each from the other because of the following reasons:

These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Each primer sequence and nucleotide residue are patentably distinct because they are unrelated sequences, i.e. these sequences are unrelated because each has a different nucleotide composition and as a result different physical and biochemical properties and differs in structure and in function and in biological activity, while primers do not encode proteins, their ability to hybridize and subsequently prime amplification is a direct effect of their characteristic nucleic acid arrangement. The Examiner reaffirms that the groups are properly separated as their inclusive products are comprised by different nucleic acid sequences and as a result, create distinct groups with variant structural and functional capacities. The examiner maintains the restriction requirement made previously, as each group is correctly separated as unrelated or patentably distinct and as such make the requirement final."

Claim Interpretations

It should be noted that the claim language including "selectively hybridize under highly stringent conditions" is interpreted as being able to hybridize under any sort of high stringency conditions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-7, 20-22, 25, 31, 37-39, 43-44, 46-49, 59, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170).

With regard to claim 1, Klinger et al. teach a primer comprising a 5' region and adjacent 3' region, said region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence and, optionally, to a PKD1 gene homolog sequence, and said 3' region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence, and not

to a PKD1 gene homolog sequence, provided the primer does not consist of a sequence as set forth in SEQ ID NO:11, 18, 52, and 60(Abstract, Col. 5 lines 45-67 – Col. 6 1-4 and figure 3B).

With regard to claims 2-4, Klinger teaches the above primer wherein said 5'region comprises at least about ten contiguous nucleotides, wherein the 3'region comprises at least one 3'terminal nucleotide identical to a nucleotide that is 5' and adjacent to the nucleotide sequence of the PKD1 gene to which the 5' region of the primer can hybridize, and wherein said 3' terminal nucleotide is different from a nucleotide that is 5' and adjacent to a nucleotide sequence of the PKD1 homolog to which the 5' region of the primer can hybridize wherein the 3' region comprises about 2 to 4 3' terminal nucleotides and a 5' region of about 14 to 18 nucleotides and a 3' region of about 2 to 6 nucleotides in their teaching of the primer in Figure 3B of 5'AGGACCTGTCCAGGCATC 3'.

With regard to claims 5-7, Klinger teaches in Col. 5, that the "present invention encompasses isolated oligonucleotides corresponding to sequences within the PKD1 gene and PKD1cDNA, which, alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences. These oligonucleotides may be from about 12 to about 60 nucleotides in length, preferably about 18 nucleotides; may be single or double stranded, and may be labeled or modified as described below. An example of an oligonucleotide that can be used in this manner is shown in Fig. 3B"(Col. 5). (Note: art has been applied according to the specification's definition of "substantially identical" on page 21, a primer with "at least about 80% identity to one of SEQ ID NOS: 3 to 51 and 61 to 113")

With regard to claim 20, 59, and 62, Klinger et al. teach an isolated polynucleotide, comprising a contiguous sequence of at least about ten nucleotides substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto, the contiguous nucleotide sequence comprising a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted(Col. 5 lines 45-67 and Col. 6 lines1-17). Furthermore, the reference teaches that "deletions may be detected using a PCR-based assay , in which pairs of oligonucleotides are used to prime amplification reactions and the sizes of the amplification products are compared with those of control products"(Col. 8 lines 36-40).

With regard to claims 21 and 22, Klinger et al. teach the above polynucleotides in a vector and furthermore the host cell transformed by this vector. The abstract teaches that "the invention also encompasses vectors comprising these nucleic acids, host cells transformed with the vectors"(+ Col. 6 lines 39-67 and Col. 7 lines 1-15).

With regard to claim 25 and 43, Klinger et al. teach a method of detecting the presence or absence of a mutation in a PKD1 polynucleotide in a sample, the method comprising: contacting nucleic acid molecules in a sample with at least one primer pair of claim 7 under conditions suitable for amplification of a PKD1 polynucleotide by the primer pair, thereby generating a PKD1-specific amplification product, under said conditions; and identifying the presence or absence of a mutation in the PKD1-specific amplification product, thereby detecting the presence or absence of a mutation in the PKD1 polynucleotide in the sample(See for example Col. 8 lines 35-60 and Col. 9 lines 47-67 and Col. 10 lines 1-40).

With regard to claim 31, Klinger et al. further teach the above method of identifying the presence or absence of a mutation in the amplification product comprises determining the

nucleotide sequence of the amplification product as taught in the embodiment of the assay used to detect the presence of mutation in Col. 10 for example of "direct DNA sequencing" line 35(+ Col. 8 lines 35-38).

With regard to claim 37, 44 and 49 Klinger et al. teach the method of detecting a presence or the absence of a mutation wherein a primer extension assay is used and performed with a detectably labeled primer(Col. 5 line 52) and a mixture of deoxynucleotides and dideoxynucleotides(sequencing and also see Col. 14 lines 1-10), and wherein the primer are selected so as to enable differential extension of the primer in the presence of a wild-type PKD1 polynucleotide as compared to a mutant PKD1 polynucleotide. Although the sequencing method taught by the reference(Col. 10 line 35) teaches the limitation of claim 37, the PCR reaction of Cols 13 and 14 also anticipate the limitation of 37 and 44 in their use of a sample from a subject("whole blood samples" Col. 12 line 63) to obtain their data.

With regard to claims 38, 39, and 48 Klinger teaches that the above method is performed both using a plurality of primer pairs and in a high throughput format utilizing a plurality of samples(Col. 11, lines 11-17).

With regard to claims 46-47 wherein identifying the presence or absence of a mutation in the amplification product is associated with the PKD1-associated disorder autosomal dominant polycystic kidney disease(Col. 1 lines 10-49).

Klinger et al. does not teach in Figure 3, a primer that is extendable on its 3' because of a polymerization blocking agent.

However, Klinger et al. do teach both the authentic PKD1 sequence, the homolog PKD1 sequence, and primers to amplify both of these and to amplify preferentially the authentic

sequence alone. Furthermore, the reference in Column 8 lines 46-60 teaches that a "confounding and complicating factor in the detection of a PKD1 mutation is the presence of PKD1 homologues at several sites on chromosome 16" and that in "analysis of mutations in PKD1, it is critical to distinguish between sequences derived from any of the homologues".

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have practiced the teachings of Klinger et al. to have obtained a primer as claimed capable of differentiating between the authentic and homolog PKD1 sequence for their provided expected benefit that "an important feature of the present invention is the provision of oligonucleotide primers that discriminate between authentic PKD1 and the homolgues"(Col. 8 line 53-55). The reference goes on to teach that "a detailed comparison of the sequences of the authentic PKD1 gene and the homologues enables design of primers that discriminate between the authentic PKD1 gene or cDNA and the homologues"(Col. 8 line 55-60). Thus, in light of these teachings of the desirability of making primers that are able to discriminate between the PKD1 gene sequence and the PKD1 homolog, it would have been obvious for one of ordinary skill in the art at the time the invention was made to have used the sequence of Figure 3A to make primers with a free 3' hydroxyl group through which subsequent extension of a non-homolog sequence could be achieved during an amplification reaction.

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive.

After summarizing their invention, applicant first argues that "the claims require that a primer of the invention includes a 3' region that selectively hybridizes to PKD1, but not to a PKD1 homolog and therefore, knowledge of a sequence that is present in authentic PKD1, but not in a

homolog". However, the claim requires only that the 5' end of their primer hybridize minimally to any PKD1 sequence and that the 3' end hybridize to s PKD1 gene sequence as well, but not to a PKD1 gene homolog sequence. Given the sequence discussed in the interview of Figure 3A and the teaching of the patent's disclosure in making primers to differentiate between the homolog and the WT PKD1 gene sequences, a primer could be made that meets this limitation, since hybridization to a sequence in common between the WT and homolog is not hybridizing only to a sequence present in a homolog. The claim as presently written only requires that the 3' region selectively does not hybridize to a PKD1 gene homolog sequence, it does not preclude the hybridization of the 3' end to a sequence that both the WT and homolog sequence share in common, i.e. not had solely by the homolog sequence(e.g. ccaggcatcacagccg). Applicants further argue that "Klinger et al. do not teach or suggest a sequence of authentic PKD1 that is not present in the homolog sequence", but it is asserted that this requirement is not in applicant's claims as presently written. It is again noted that only the requirement in the claims is that hybridization "not to a PKD1 gene homolog sequence" is noted for the 3' end of the primer. In the absence of explicit definitions in the specification(for a PKD1 gene homolog sequence), "not to a PKD1 gene homolog sequence" is not interpreted as being the same as "a sequence of authentic PKD1 that is not present in the homolog sequence". Instead, as pointed out above, it is interpreted that the portion(e.g. ccaggcatcacagccg) shared in common between the two sequences is "not to a PKD1 gene homolog sequence" since it is also to the WT PKD1 gene sequence. Applicant is reminded limitations in applicant's arguments, specification etc cannot be read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, this rejection is being maintained since applicant's amendments to the claims

makes indefinite their invention(see new 112 2nd rejection below) as it is not required that the entire set of primers be inclusive of all of claim 1's requirements(i.e. a set is not required). Next applicant argues that Klinger et al. does not "refer to specifically to any of the claimed polynucleotides". However, in Col. 5 lines 42-44 the reference teaches a 5' cDNA fragment comprising 894 bases spanning nucleotides 3393-4287, therefor anticipating the nucleotide at 3336. The method's teaching of deletions in Col. 5 lines 45-67 and Col. 6 lines1-17) and furthermore in the teaching that "deletions may be detected using a PCR-based assay , in which pairs of oligonucleotides are used to prime amplification reactions and the sizes of the amplification products are compared with those of control products"(Col. 8 lines 36-40) anticipates this limitation.

2. Claims 16-17, 19, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Stefano(US Patent 6,297,010).

While the teachings of Klinger et al. can be read above, the reference does not teach the limitation of claims 16-19 and 40 and 42 that include the primers immobilization on a solid matrix such as a microchip or an array.

However, Stefano teaches high density arrays of bound nucleotides used in methods for "high-throughput analysis of DNA, i.e., the rapid and simultaneous analysis of DNA, i.e., the rapid and simultaneous processing of DNA samples derived from a large number of patients"(Column 16 lines 57-65). The reference teaches a "method for identification of one or more mutation(s) in a sample polynucleotide by immobilizing a plurality of sample polynucleotides on a single solid support"(Col. 4 lines 40-44). The reference further provides

that the solid support may be matrices such as "treated or untreated microtiter plates" or in the case of "amino-modified PCR products can be bound to silylated glass surfaces"(Col. 12 lines 11-45).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger's method and primers and practiced them on the solid support of Stefano since the "cost and labor required to sequence every patient DNA sample over these important regions would make the detection of pathogenic mutations extremely slow and prohibitively expensive"(Col. 3 lines 9-20) and for the expected benefit that their method provides that "both indicates the presence of unknown mutations and which directly provides the sequence alterations"(Col. 3) through their high-throughput analysis of DNA.

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

3. Claims 8-15, 26, 28, 29, 54, 68-72, and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536).

While the teachings of Klinger et al. can be read above, with regard to Claims 8-15, 26, 28, 29, 54, 68-72, and 74, Klinger et al. teach SEQ ID NO:1, which includes all of the SEQ ID NOS of 3, 4, 19 and 20(See attached alignments). While Klinger et al. define their 31,571 base

pair sequence as the PKD1 genomic sequence and furthermore teach the "isolated oligonucleotides corresponding to sequences within the PKD1 gene or within the PKD1 cDNA, which alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences"(Col. 5, lines 40-55) and also "an example of an oligonucleotide that can be used in this manner(See Fig. 3B); Klinger does not teach the primer sequences of SEQ ID NOS of 3, 4, 19 and 20, only the sequences in the genomic form of their SEQ ID NO:1(see alignments).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected the primers of SEQ ID NOS: 3, 4, 19 and 20 from the Klinger's known sequence of SEQ ID NO: 1 for the expected benefit of obtaining functionally equivalent primers with the ability to "selectively prevent the amplification of PKD1 homologue sequences. In this manner authentic PKD1 sequences are selectively amplified"(Col. 5 lines 64-67)

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of PDK1,

and in particular for the detection of the authentic sequence of PDK1 not homologs, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive.

Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

4. Claims 27, 53, 55, 60, 61, 73, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Shapira et al.(PNAS 1991)

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claims 27, 53, 55, 60, 61, 73, and 75 that includes the nesting of primer pairs one inside the other.

However, Shapira et al. teach a method of amplifying nucleic acids by way of nested primer pairs. The reference teaches that following a first round of PCR, "a second round of PCR utilizing the nested primers in Fig. 2 in a reaction mixture containing the same concentrations of all of the above constituents, except for 1.5 mM MgCl2 and a 5ul aliquot of the previous PCR reaction mixture that served as the DNA template"(Pg. 7529 left).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the nesting of primer pairs teachings of Shapira with nested the SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the expected benefit that "nested-primer PCR provided the sensitivity to analyze...that was not available with Southern blotting techniques"(Pg. 7528 right).

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

5. Claims 32-33 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Sathe et al.(US Patent 6,362,326).

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claims 32-33 and 35-36 that include the use of temperature melting, HPLC, and SSCP analysis on the amplification products in order to identify the presence or absence of a mutation.

However, Sathe et al. teach the detection of mutations on the DNA level through "single-stranded conformation polymorphism assay (SSCA or SSCP)"(Col. 8 lines64-65). The references continues to teach that the "increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10). Even further, "denaturing HPLC, similar to SSCP, can be used which uses a PCR amplified product, run down a heated HPLC column; the heating disassociates the DNA strands and one usually sees two peaks if there is a variation in allelic forms"(Col. 9 lines 14-18) "and it works on the same principles as SSCP"

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sathe's SSCA and HPLC in mutation detection to method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the expected benefit of these techniques being a "viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10).

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

6. Claims 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Iliff (US Patent 6,234,964).

While the teachings of Klinger can be seen above, the reference does not teach the limitations of claims 50-52 including transmitting a report to a user via internet, fax or mail.

However, Iliff teach a disease management system that "gives the patient the option of receiving a summary of the consultation session and specific recommendations provided by the system via facsimile, electronic mail, or mail service"(Col. 12 lines30-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger's method and primer and transmitted their resulting data through a report to a user using a fax, e-mail, or regular mail of Iliff for the expected benefit of "promoting patient health in an automated manner that reduces costly medical intervention"(Abstract).

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

7. Claims 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Shapira et al.(PNAS 1991) in further view of Sathe et al.(US Patent 6,362,326).

While the teachings of Klinger et al. in view of Buck et al. and in a further view of Shapira et al. can be read above, but the three references do not teach the limitation of claims 55-57 of temperature melting, HPLC, and SSCP analysis on the amplification products in order to identify the presence or absence of a mutation.

However, Sathe et al. teach the detection of mutations on the DNA level through "single-stranded conformation polymorphism assay (SSCA or SSCP)"(Col. 8 lines64-65). The references continues to teach that the "increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10). Even further, "denaturing HPLC, similar to SSCP, can be used which uses a PCR amplified product, run down a heated HPLC column; the heating disassociates the DNA strands and one usually sees two peaks if there is a variation in allelic forms"(Col. 9 lines 14-18) "and it works on the same principles as SSCP"

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sathe's SSCA and HPLC in mutation detection to the nested primer pair method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck and in further view of Shapira for the expected benefit of these techniques being a "viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10).

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

8. Claims 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Ahern et al.(The Scientist, 1995)

While the teachings of Klinger et al are summarized above, the reference does not teach a kit for detecting the presence or absence of a mutation in a PKD1 gene,

However, Ahern teaches that "biochemical, reagents kits offer scientists good return on inventment" as combining the reagents into a kit form offers scientists "the opportunity to better manage their time, putting these products all together in kits takes the convenience one step further"(Pg. 4 top).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger's primers and methods into a kit taught by Ahern for the expected benefit of "buying premade reagents and kits because they are convenient and they save time"(Pg. 4).

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

9. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Koster et al.(US Patent 6,225,450).

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claim 34 that includes the use of matrix-assisted laser desorption time of flight mass spectrometry on the amplification products in order to identify the presence or absence of a mutation.

However, Koster et al. teach a method of "DNA sequencing that utilizes the sanger sequencing strategy and assembles the sequence information by analysis of the nested fragments obtained by base-specific chain termination via their different molecular masses using mass spectrometry as for example Maldi(Abstract)" The reference further teaches that "MALDI can be particularly attractive when a time of flight (TOF) configuration is used as a mass analyzer"(Col. 6 lines 45-47).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Koster's MALDI TOF method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the expected benefit of these techniques providing a "high speed, high throughput, no electrophoresis and gel reading artifacts...and no costly reagents involving various substitutions with stable isotopes"(Abstract).

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive. Since applicant did not provide any additional substantive arguments other than those that were previously addressed above, no additional response to arguments is provided.

35 U.S.C. 112, Written Description Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-4,6-11,16,17,19-29,31-37,39-57,59-63,65,66,68,69 and 72-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

The specification discloses SEQ ID NO: 1 which the specification asserts corresponds to the wt PKD1 gene(pg. 26). Claims 1-66 and 68-75 are directed to encompass sequences comprising nucleotides that selectively hybridize to a PKD1 gene sequence and optionally to a PKD1 homolog sequence, primers comprising regions wherein at least 10 contiguous nucleotides that "can hybridize", primers comprising regions which "can selectively hybridize to a nucleotide sequence flanking and within about fifty nucleotides", primers comprising a nucleotide sequence substantially identical to any of SEQ ID NOS 3, 4, 19, or 20, primers which can amplify a portion of SEQ ID NO:1 comprising about nucleotides 2043 to 4209, etc. For example, claim 7 as written could encompass any T3 and T7 primer pair that "can amplify" a cloned region of SEQ ID NO:1 comprising about nt 2043 to 4209. Thus, the instant claims encompass nucleic acids and methods that comprise any number of potential sequences when one considers that they encompass nucleic acids that comprise partial matches to the recited SEQ ID numbers and the ability to "hybridize" to and "can amplify" even more sequences. This genus can read on any number of possible primers comprising any number of known and unkown nucleic acid fragments, yet the specification has only disclosed the nucleic acids of SEQ ID NO: 1 and primers of SEQ ID NOS: 3, 4, 19, and 20. A review of the full content of the

specification indicates that the sequence of nucleotides of SEQ ID NO: 1 and all aforementioned variations, are essential to the operation and function of the claimed invention. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 1, 3, 4, 19 and 20, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The named ORF is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for isolating and characterizing cDNA sequences from *E. grandis*, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe *E. grandis* cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the specification does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute *E. grandis* cDNA appears in the application. Accordingly, the specification does not provide a written description of the invention of claims 1, 4, and 6-15.

Therefore, none of the sequences encompassed by the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Response to Arguments:

Applicant's arguments filed 11/26/2004 have been fully considered but they are not persuasive.

While applicant's attempted clarification conferred in adding "highly stringent conditions" is noted and further applicant's assertion of their structural and functional definitions of the claimed subject matter is also noted, neither are able to remedy the still present lacking written description. Applicant is reminded that for example, claim 7 as written could encompass any T3 and T7 primer pair that "can amplify" a cloned region of SEQ ID NO:1 comprising about nt 2043 to 4209. Thus, the instant claims encompass nucleic acids and methods that comprise any number of potential sequences when one considers that they encompass nucleic acids that

comprise partial matches to the recited SEQ ID numbers and the ability to "hybridize" to and "can amplify" even more sequences. The new requirement for "highly stringent conditions" adds no structural component to the claims. Applicant may consider amending the claims to include the actual SEQ ID NOS: of the 8 primers in the set to which they referred in the recent telephone interview, instead of the genus of primers presently recited.

---NEW REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS---

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-4,6-11,16,17,19-29,31-37,39-57,59-63,65,66,68,69 and 72-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-4,6-11,16,17,19-29,31-37,39-57,59-63,65,66,68,69 and 72-75 are indefinite over the recitation of "a set of primers, comprising primers" and "wherein a primer of said set". It is not clear if applicant intends to claim the entire set of 8, or instead a single primer of the set. While in the interview taking place on 10/22/2004, it was suggested to the applicant that the inclusion of the entire set of 8 primers could obviate the rejections of the claims, it is presently unclear what applicant intends to claim(i.e., the set of 8 or a single primer?) as the claim is contradictory presently in its requirements. Appropriate correction is required.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (571)272-0748. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Jeffrey Fredman, can be reached at (571)272-0742. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782. The official fax number is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (571)272-0518.

Sally Sakelaris

2/17/2005

JEFFREY FREDMAN
PRIMARY EXAMINER
2/17/05